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A HYPOGLYCEMIC AGENT

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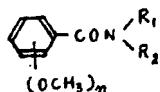
Specification

1. Title of Invention

Hypoglycaemic agent

2. Patent Claim

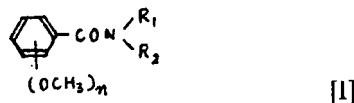
Hypoglycemic agent which has a compound represented by the following formula as the active component.



[In the formula, R₁ denotes hydrogen atom or lower alkyl group, R₂ denotes a linear, branched or cyclic alkyl group, a pyridyl group which may have a substituent on the nucleus or a pyridylmethyl group, and n denotes 1-3].

3. Detailed Description of the Invention

This invention is the invention of a hypoglycemic agent which has a compound represented by the following formula (I) as the active component



[In the formula, R₁ denotes hydrogen atom or lower alkyl group, R₂ denotes a linear, branched or cyclic alkyl group, a pyridyl group which may have a substituent on the nucleus or a pyridylmethyl group, and n denotes 1-3].

Known compounds are included in the aforesaid compound represented by the formula (I), but in the previous literature in which they are mentioned, there is no mention at all of a hypoglycemic effect or a pharmacological action suggesting this.

The compounds of this invention represented by the aforesaid formula (I) may be obtained readily by usual methods of reacting an amine compound with a methoxybenzoyl chloride compounds in the presence of a base such as triethylamine, as illustrated in the following reference example.

Reference Example

4-methoxybenzoyl chloride 17 g was added gradually under ice cooling and stirring to a mixed solution of 3-aminopyridine 9.4 g, triethylamine 15ml and acetone 200 ml. After stirring for 30 minutes at the same temperature then for 60 minutes at room temperature, the reaction solution was poured into 1 l of water, and the crystals which precipitated were collected by filtration and washed with water, then re-crystallised from methanol, to obtain 175 g of colourless acicular crystals of 4-methoxy-N-3-pyridylbenzamide (compound 1), melting point 168-170°C.

Elemental analysis	as molecular formula C ₁₃ H ₁₂ N ₂ O ₂		
	C	H	N
theoretical value (%)	68.41	5.30	12.27
experimental value (%)	68.33	5.27	12.24

The compounds of Table 1 were obtained in the same way.

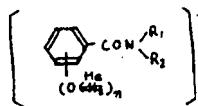


Table 1

No.	-(OMe) _n	R ₁	R ₂	Molecular formula	Melting point (°C)	Yield (%)	Elemental anal. values		
							Calc(%)	C (%)	H (%)
						Found(%)	C	H	N
2	2-OMe	H		$O_1H_{12}N_2O_2$	112~114	7.6	68.41 68.49	5.30 5.24	12.27 12.31
3	-	-		$O_1H_{14}N_2O_2$	80~82	8.3	69.40 69.32	5.83 5.80	11.56 11.59
4	-	-		$O_1H_{15}N_2O_2$	85~87	9.1	70.29 70.24	6.29 6.23	10.93 10.99
5	3-OMe	-		$O_1H_{13}N_2O_2$	121~122	8.5	68.41 68.48	5.30 5.36	12.27 12.21
6	-	-		-	155~156	8.9	68.43 68.43	5.31 5.31	12.30
7	-	-		$O_1H_{14}N_2O_2$	99~101	8.8	69.40 69.47	5.83 5.79	11.56 11.60
8	4-OMe	-		$O_1H_{13}N_2O_2$	131~132	7.9	68.41 68.35	5.30 5.26	12.27 12.31
9	-	-		$O_1H_{14}N_2O_2$	150~153	6.5	69.40 69.36	5.83 5.79	11.56 11.52
10	-	-		-	71~73	6.8	69.40 69.47	5.83 5.78	11.56 11.58
11	-	-		-	61~64	7.7	69.40 69.45	5.83 5.88	11.56 11.63
12	-	-		$O_1H_{16}N_2O_2$	136~137	8.2	70.29 70.37	6.29 6.34	10.93 10.89
13	2,3-(OMe) ₂	H		$O_1H_{14}N_2O_3$	117~118	5.8	65.10 65.14	5.46 5.49	10.85 10.91
14	-	-		$O_1H_{16}N_2O_3$	110~111	6.2	66.16 66.12	5.92 5.95	10.29 10.33
15	-	-		$O_1H_{15}N_2O_3$	111~112	6.7	67.11 67.14	6.34 6.37	9.78 9.75
16	2,4-(OMe) ₂	-		$O_1H_{16}N_2O_3$	98~99	5.1	66.16 66.11	5.92 5.87	10.29 10.34
17	-	-		-	140~141	6.9	66.16 66.21	5.92 5.96	10.29 10.31
18	-	-		$O_1H_{15}N_2O_3$	93~94	6.3	67.11 67.15	6.34 6.39	9.78 9.74
19	2,6-(OMe) ₂	-		$O_1H_{16}N_2O_3$	155~156	6.7	66.16 66.22	5.92 5.97	10.29 10.24
20	-	-		$O_1H_{16}N_2O_3$	206~209	6.3	67.11 67.07	6.34 6.39	9.78 9.80
21	3,4-(OMe) ₂	-		$O_1H_{14}N_2O_3$	84~86	7.9	65.10 65.16	5.46 5.41	10.85 10.87
22	-	-		-	49~51	8.8	65.10 65.08	5.46 5.43	10.85 10.88
23	-	-		$O_1H_{16}N_2O_3$	122~123	6.3	66.16 66.12	5.92 5.97	10.29 10.24
24	-	-		-	128~129	7.4	66.16 66.19	5.92 5.88	10.29 10.33
25	-	-		-	131~132	7.5	66.16 66.20	5.92 5.96	10.29 10.25

2 6	3,4-(OMe) ₂	H		C ₁₆ H ₁₈ N ₂ O ₃	69~71	63	6.7.1.1	6.3.4	9.7.8
2 7	-	-	i-Pr	C ₁₂ H ₁₇ NO ₃	144~145	85	6.4.5.5	7.6.8	6.2.7
2 8	-	-	n-Bu	C ₁₃ H ₁₉ NO ₃	83~84	88	6.4.5.9	7.6.1	6.2.3
2 9	-	-	n-Bu	-	127~128	63	6.5.8.0	8.0.7	5.9.0
3 0	-	-	t-Bu	-	124~125	80	6.5.8.0	8.0.7	5.9.0
3 1	-	-		C ₁₅ H ₂₁ NO ₃	181~182	91	6.8.4.1	8.0.4	5.3.2
3 2	3,5-(OMe) ₂	-		C ₁₈ H ₂₀ N ₂ O ₃	96~97	85	6.6.1.6	5.9.2	10.2.9
3 3	-	-		C ₁₆ H ₁₈ N ₂ O ₃	119~120	87	6.7.1.1	6.3.4	9.7.8
3 4	3,4,5-(OMe) ₃	-		C ₁₈ H ₂₀ N ₂ O ₄	154~156	65	6.2.4.9	5.5.9	9.7.2
3 5	-	-		-	157~158	77	6.2.5.2	5.5.6	9.7.3
3 6	-	-		C ₁₆ H ₁₈ N ₂ O ₄	115~116	58	6.3.5.6	6.0.0	9.2.7
3 7	-	-		-	145~146	69	6.3.5.6	6.0.0	9.2.7
3 8	-	-		-	127~128	84	6.3.5.6	6.0.0	9.2.7
							6.3.5.9	6.0.3	9.2.9

3 9	3,4,5-(OMe) ₃	H		C ₁₇ H ₂₀ N ₂ O ₄	145~146	71	6.4.5.4	6.3.7	8.8.6
4 0	-	-	n-Pr	C ₁₃ H ₁₉ NO ₄	114~115	73	6.1.6.4	7.5.6	5.5.3
4 1	-	-	i-Pr	-	154~155	77	6.1.6.4	7.5.6	5.5.3
4 2	-	-	n-Bu	C ₁₄ H ₂₁ NO ₄	133~134	80	6.2.9.0	7.9.2	5.2.4
4 3	-	-	n-Bu	-	162~163	75	6.2.9.0	7.9.2	5.2.4
4 4	-	-	t-Bu	-	133~134	79	6.2.9.0	7.9.2	5.2.4
4 5	-	-	t-Bu	-	122~123	81	6.2.9.0	7.9.2	5.2.4
4 6	-	-		C ₁₈ H ₂₀ NO ₄	182~183	88	6.5.5.1	7.9.0	4.7.8
4 7	-	i-Pr	i-Pr	C ₁₆ H ₂₆ NO ₄	127~128	72	6.5.0.6	8.5.3	4.7.4
							6.5.1.1	8.5.9	4.7.1

The compounds of this invention obtained in this way have excellent hypoglycemic action, and are effective at 100 mg/kg in man, and their effect is maintained by administration of 0.1-100 mg once a day for 24 hours or more.

For administration, a preparation is used which has been formed into the desired form by a customary means normally used in drug formulation.

Example 1

5-week-old mice (male, body weight 25-30g) with 5 animals in a group were fasted for 16 hours, and then alloxan at 75 mg/kg was administered intravenously. After 48 hours, a solution or suspension of a compound of this invention (200 mg/kg) was administered orally, and after 150 minutes, blood was taken from the heart and the glucose level was measured using glucose oxidase. The measurement results are exemplified in Table 2.

Table 2

Administered compound	Blood glucose value (mg/dl) mean \pm S.D.
None (control)	473 \pm 28
1	326 \pm 42 **
3	378 \pm 31 **
4	364 \pm 19 ***
6	378 \pm 52 *
7	412 \pm 33 *
12	383 \pm 28 **
17	345 \pm 41 ***
22	378 \pm 37 **
25	355 \pm 46 **
26	336 \pm 32 ***
27	407 \pm 30 *
28	402 \pm 24 **
29	421 \pm 27 *
32	416 \pm 23 *
33	402 \pm 34 *
36	416 \pm 21 **
38	307 \pm 43 ***
39	412 \pm 31 *
41	421 \pm 28 *
46	383 \pm 41 **

* : P < 0.05 , ** : P < 0.01 , *** : P < 0.001

In the Table, the compound number corresponds to the compound number of the reference examples.

Example 2

4-methoxy-N-3-pyridylbenzamide (compound 1)	100 parts
calcium hydrogen phosphate	58.5 parts
crystalline cellulose	50 parts
corn starch	40 parts
calcium stearate	1.5 parts

These components were mixed well and pressed into 250 mg tablets (content of active component 100 mg/tablet) by usual methods, for use as a hypoglycemic agent.

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